Thromboembolic disease of the venous and the arterial system

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Chapter 8

Venous thromboembolism as a risk factor for subsequent arterial thromboembolism: Results from the Prevention of Renal and Vascular End-stage Disease (PREVEND) Study

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ABSTRACT

Context: Evidence on the relation between venous and arterial thromboembolism is inconsistent. Furthermore, age and other cardiovascular risk factors were not always taken into account.

Objective: To determine the risk of arterial thromboembolism after venous thromboembolism, independent of cardiovascular risk factors.

Design, Setting, and Participants: In 1997-1998, inhabitants of the city of Groningen, the Netherlands, aged 28-75 years (n=85,421), were sent a questionnaire on cardiovascular risk factors, and a vial to collect a urine sample. After entry, all responding subjects (n=40,856) were followed and monitored for venous and arterial thromboembolism. Median follow-up time was 7.8 years. Thromboembolism was verified with national registries of hospital discharge diagnoses and death certificates, the regional anticoagulation clinic and medical records.

Main Outcome measure: Arterial thromboembolism (ie, myocardial infarction, coronary artery disease, peripheral arterial occlusive disease, or ischemic stroke) between study initiation and December, 31, 2005.

Results: Of 40,856 responding subjects (46% male; median age at enrollment, 48 years), 410 developed venous thromboembolism (42% unprovoked), and 2314 developed arterial thromboembolism during a median follow-up period of 7.8 (interquartile range, 7.5-8.1) years. Annual incidence of arterial thromboembolism after venous thromboembolism was 2.36% (95% confidence interval [CI], 1.59-3.37), compared to 0.80% [95% CI, 0.77-0.83] in subjects without venous thromboembolism. Adjusted hazard ratio of arterial thromboembolism after venous thromboembolism was 1.81 [95% CI, 1.26-2.60]. This risk was highest within the first year after venous thromboembolism (annual incidence, 3.51% [95% CI, 1.81-6.13]; adjusted hazard ratio, 2.58 [95% CI, 1.46-4.55]) and after an unprovoked event (annual incidence, 2.78% [95% CI, 1.62-4.45]; adjusted hazard ratio, 1.94 [95% CI, 1.20-3.12]).

Conclusions: Subjects with venous thromboembolism are at a high risk to develop arterial thromboembolism, independent of age and other cardiovascular risk factors. This risk is particularly high in the first year after venous thromboembolism and after an unprovoked event.

INTRODUCTION

The concept that venous and arterial thromboembolism are separate pathophysiological entities has been challenged.[1] In 2003, Prandoni et al. were the first to report a twofold increased risk for unprovoked deep vein thrombosis in patients with atherosclerotic plaques.[2] More recently, a large case-control study showed a 2-3 fold increased relative risk of arterial thromboembolism after first venous thromboembolism, most predominantly in the first year following initial venous thromboembolism.[3] However, evidence on the relation between venous and arterial thromboembolism is inconsistent. Two observational studies could not identify an increased risk of overall or unprovoked venous thromboembolism in patients with atherosclerosis.[4,5] Furthermore, age effects were not fully taken into account in all studies that considered venous and arterial thromboembolism as two related diseases.[6-9] Age is a strong confounder to the risk of both venous and arterial thromboembolism, hence it is doubtful whether the high absolute risk of arterial thromboembolism after venous thromboembolism (reported to be as high as 5.5% per year),[8] is truly related to previous venous thrombotic disease or merely a result of ageing. In addition, previous studies did not always correct for the presence of cardiovascular risk factors.[3] This is remarkable as these factors (i.e. elevated albuminuria, hypertension, dyslipidemia, diabetes mellitus, and smoking) are also reported to be associated with venous thromboembolism.[6,10]

This study was conducted to advance our understanding of both venous and arterial thrombotic disease and to provide further insight into the clinical course of patients with venous thromboembolism. Our aims were to determine the absolute risk of arterial thromboembolism after venous thromboembolism, and to establish whether venous thromboembolism is a risk factor for subsequent arterial thromboembolism, independent of age, sex and other cardiovascular risk factors, in a population-based cohort of more than 40,000 subjects.

METHODS

Study population

This study was conducted on participants in the Prevention of REnal and Vascular ENd stage Disease (PREVEND) study. The PREVEND study was designed to prospectively investigate the natural course of albuminuria and its relation with renal and cardiovascular disease in a large cohort drawn from the general population. Details of this study have been published previously[11] and can be found at http://www.prevend.org. In 1997-1998, all inhabitants of the city of Groningen, the Netherlands, aged 28 to 75 years (n=85421) were sent a postal questionnaire and a vial to collect an early morning urine sample. A total of 40,856 subjects (47.8%) responded. The questionnaire provided information about the presence of established risk factors for cardiovascular disease. Subjects were classified as being diabetic when they positively answered the question whether they were diagnosed with diabetes by a physician, regardless of the type of antidiabetic treatment. Subjects were considered hypertensive or dyslipedemic when they positively answered the question whether high blood pressure or high cholesterol, respectively, had ever been measured. Those who reported smoking or having smoked cigarettes during the previous 5 years were regarded as smokers. A history of myocardial infarction or stroke was considered present if associated with a hospitalization for at least 3 days.

All participants gave written informed consent. The PREVEND study was approved by the local medical ethics committee and was conducted in accordance with the guidelines of the Declaration of Helsinki.

Measurements

Morning urinary albumin concentration (UAC) was established by a commercial immunoturbidimetry assay with sensitivity of 2.3 mg/L and inter- and intra-assay coefficients of variation of 2.2 and 2.6%, respectively (BN II, Dade Behring Diagnostica).[11,12] First morning urine was used for analysis. Urine samples could be analyzed for 40,854 subjects. Albuminuria was considered elevated at a concentration of 20 mg/L or more.

Definition of thrombotic events

To identify subjects with thromboembolism between January 1997 and December 2005, the databases of the national registry of hospital discharge diagnoses (Prismant, Utrecht, the Netherlands) and death certificates (Central Bureau of Statistics, The Hague/Heerlen, the Netherlands) were used. Previous reports have shown that the Prismant-database is of good quality, with 84-87% of the Prismant diagnoses matching the diagnoses found in the patient chart.[13,14] Venous events were verified with the database of the regional anticoagulation clinic, which monitors the anticoagulant therapy of all inhabitants of the city of Groningen and environs. For further corroboration, patients' medical records were examined for all subjects with venous thromboembolism according to any of the abovementioned databases. Arterial thromboembolism was defined as myocardial infarction, coronary artery disease, peripheral arterial occlusive disease, and ischemic stroke. Deep vein thrombosis had to be confirmed by compression ultrasound, and pulmonary embolism by ventilation/perfusion lung scanning, spiral computed tomography, or at autopsy. Venous thromboembolism was classified as being provoked when it had occurred at or within 3 months after exposure to an exogenous risk factor including surgery, trauma, immobilization for more than 7 days, pregnancy, puerperium, the use of oral contraceptives or hormonal replacement therapy, or malignancy. Venous thromboembolism was classified as unprovoked when no such exogenous risk factor occurred.

Statistical analysis

We estimated the absolute risk of arterial thromboembolism in subjects with and without venous thromboembolism to assess whether venous thromboembolism is a risk factor for arterial thromboembolism. The absolute risk was expressed as an annual incidence and was calculated by dividing the number of arterial events by the number of years of follow-up. For subjects without venous thromboembolism, observation time started at time of enrollment and ended at time of arterial thromboembolism, a censoring event (intracranial arterial bleeding, death, moving out of the city) or end of study (December 2005). For subjects who had venous thromboembolism, observation time started at time of diagnosis and also ended at time of arterial thromboembolism, a censoring event or end of study. The 95% confidence intervals (CIs) around the annual incidences were assessed with the Poisson distribution assumption. A time-varying exposure Cox proportional hazard model was used to estimate whether venous thromboembolism was a risk factor for arterial thromboembolism. Adjustments were made for age, sex, hypertension,

dyslipidemia, diabetes mellitus, smoking status, elevated albuminuria and history of arterial thromboembolism. Additional preplanned sensitivity analyses were performed for the first year of follow-up after venous thromboembolism and for the rest of follow-up, to investigate the persistence of venous thromboembolism as a risk factor through time. To exclude the possibility of hospitalization bias, causing patients with venous thromboembolism to have a spurious increased risk of subsequent arterial thromboembolism due to close monitoring in the period following the event, we also restricted these sensitivity analyses to hard arterial thrombotic endpoints (i.e. myocardial infarction, ischemic stroke or cardiovascular death).

Categorical data are presented as counts and percentages, continuous variables as medians with interquartile ranges (IQR). Statistical analyses were performed using SPSS version 16.0 (SPSS, Chicago, Illinois, United States) and SAS version 9.1 (SAS Institute, Inc, Cary, NC, USA).

RESULTS

Study Population

Clinical characteristics of the 40,856 participants are shown in the **Table**. Slightly more women responded than man. Median age at enrolment was 60 (IQR, 49-68) and 48 (IQR, 39-60) years for subjects with and without venous thromboembolism, respectively. Venous thromboembolism had occurred in 410 subjects at a median age of 64 years (IQR, 51-72). In 192 subjects the venous event was secondary to an external risk factor, 174 events were unprovoked. In 44 events the presence of an external risk factor was unknown. Thirty subjects with venous thromboembolism developed arterial thromboembolism at a median age of 71 years (IQR, 65-77). In the group without venous thromboembolism, 2284 subjects developed arterial thromboembolism at a median age of 68 years (IQR, 60-74). A total of 7181 subjects (107 subjects with venous thromboembolism, 7074 without) were censored at time of intracranial arterial bleeding (n=151, 0.37%), death (n=1770, 4.3%) or moving out of the city (n=5260, 12.9%). Median follow-up time was 7.8 (IQR, 7.5-8.1) years.

Table. Clinical Characteristics

	Venous thrombosis	**No venous thrombosis**
TOTAL	**410 (100)**	**40,446 (100)**
Baseline characteristics		
Male	200 (49)	18,425 (46)
Age at enrolment, y	60 (49-68)	48 (39-60)
Cardiovascular risk factors		
Hypertension	148 (36)	11,691 (29)
Dyslipidemia	65 (16)	5584 (14)
Diabetes Mellitus	12 (3)	1039 (3)
Current Smokers	151 (37)	16,997 (42)
Microalbuminuria (≥20 mg/L)	49 (12)	3151 (8)
History of arterial thromboembolism	26 (6)	1754 (4)
Characteristics during follow-up		
Thrombotic cardiovascular event	30 (7)	2284 (6)
Age at onset, y	71 (65-77)	68 (60-74)
Classification		
Myocardial infarction	14 (3)	813 (2)
Coronary artery disease	6 (1)	873 (2)
Peripheral arterial occlusive disease	4 (1)	170 (0)
Ischemic stroke	6 (2)	428 (1)

Continuous variables are presented as median (IQR), categorical variables as number (%)

Risk of arterial thromboembolism after venous thromboembolism

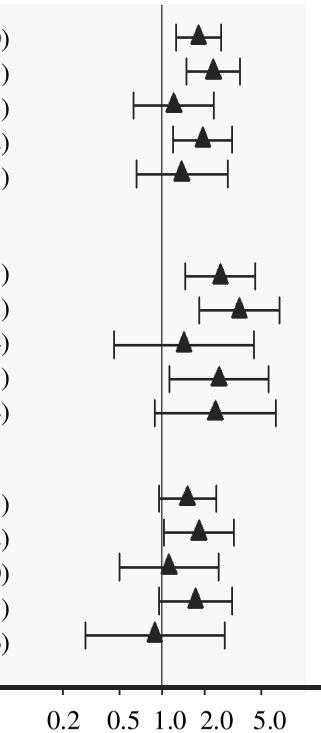
The **Figure** shows the risk of arterial thromboembolism after venous thromboembolism. The annual incidence of arterial thromboembolism after prior venous thromboembolism was 2.36% (95% CI, 1.59-3.37), compared to 0.80% (95% CI, 0.77-0.83) in subjects without venous thromboembolism. Crude hazard ratio of subsequent arterial thromboembolism was 2.90 (95% CI, 2.02-4.16) in subjects with venous thromboembolism, compared to subjects without. After adjustment for age, sex, cardiovascular risk factors and previous arterial thromboembolism, this risk was 1.81 (95% CI, 1.26-2.60). Within this model, age was a strong confounder as adjustment for age only, resulted is a hazard ratio of 1.91 (95% CI, 1.33-2.74).

When subgroups of venous thromboembolism were analyzed separately (i.e., deep vein thrombosis versus pulmonary embolism and unprovoked versus provoked venous thromboembolism), subjects with deep vein thrombosis or unprovoked venous thromboembolism had the highest risk of arterial thromboembolism, with adjusted hazard ratios of 2.30 (95% CI, 1.49-3.53) and 1.94 (95% CI, 1.20-3.12), respectively.

Risk of arterial thromboembolism was highest within the first year after venous thromboembolism with an annual incidence of 3.51% (95% CI, 1.81-6.13) and an adjusted hazard ratio of 2.58 (95% CI, 1.46-4.55). After 1 year of follow-up, the adjusted hazard ratio of arterial thromboembolism after venous thromboembolism decreased to 1.51 (95% CI, 0.95-2.41). When limited to myocardial infarction, ischemic stroke and cardiovascular death, overall adjusted hazard ratio after venous thromboembolism was 2.04 (95% CI, 1.31-3.19), and within the first year this was 2.88 (95% CI, 1.43-5.77).

Figure. Risk of arterial thromboembolism after venous thromboembolism

	Obs-yrs	No. ATE	Annual Incidence (95% CI)	Crude Hazard ratio[a] (95% CI)	Adjusted Hazard ratio[b] (95% CI)	Decreased risk for ATE	Increased risk for ATE	*P* value
OVERALL								
Venous thromboembolism (n=410)	1270	30	2.36 (1.59-3.37)	2.90 (2.02-4.16)	1.81 (1.26-2.60)			0.001
Deep vein thrombosis (n=252)	809	21	2.60 (1.61-3.97)	3.18 (2.07-4.89)	2.30 (1.49-3.53)			<0.001
Pulmonary embolism (n=158)	462	9	1.95 (0.89-3.70)	2.37 (1.23-4.57)	1.21 (0.63-2.33)			0.57
Unprovoked VTE (n=174)	612	17	2.78 (1.62-4.45)	3.40 (2.11-5.48)	1.94 (1.20-3.12)			0.01
Provoked VTE (n=192)	478	7	1.46 (0.59-3.02)	1.78 (0.85-3.73)	1.38 (0.66-2.91)			0.39
≤ 1 YEAR								
Venous thromboembolism	342	12	3.51 (1.81-6.13)	4.41 (2.50-7.78)	2.58 (1.46-4.55)			0.001
Deep vein thrombosis	209	9	4.31 (1.97-8.17)	5.41 (2.81-10.41)	3.50 (1.82-6.75)			<0.001
Pulmonary embolism	133	3	2.26 (0.47-6.59)	2.80 (0.90-8.70)	1.43 (0.46-4.44)			0.54
Unprovoked VTE	156	6	3.85 (1.41-8.37)	4.87 (2.19-10.83)	2.52 (1.13-5.63)			0.02
Provoked VTE	146	4	2.74 (0.75-7.01)	3.40 (1.28-9.05)	2.38 (0.89-6.34)			0.08
> 1 YEAR								
Venous thromboembolism	928	18	1.94 (1.15-3.07)	2.36 (1.48-3.75)	1.51 (0.95-2.41)			0.08
Deep vein thrombosis	599	12	2.00 (1.04-3.50)	2.43 (1.38-4.29)	1.82 (1.03-3.22)			0.04
Pulmonary embolism	329	6	1.82 (0.67-3.97)	2.20 (0.99-4.91)	1.12 (0.50-2.50)			0.78
Unprovoked VTE	456	11	2.41 (1.20-4.32)	2.92 (1.62-5.29)	1.72 (0.95-3.11)			0.07
Provoked VTE	332	3	0.90 (0.19-2.64)	1.09 (0.35-3.37)	0.89 (0.29-2.76)			0.84



VTE, venous thromboembolism; ATE, arterial thromboembolism; Obs-yrs, observation years

[a] Reference group are those without venous thromboembolism

[b] Reference group are those without venous thromboembolism, adjusted for age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking status, elevated albuminuria and history of arterial thromboembolism

DISCUSSION

This large population-based cohort study shows that subjects with previous venous thromboembolism are at increased risk to develop arterial thromboembolism. Although age was a strong confounder to this risk, the relative risk was still 1.8-fold increased after adjustment for age, sex, cardiovascular risk factors and history of arterial thromboembolism. The overall absolute risk was as high as 2.4% per year and 3.5% within the first year after venous thromboembolism was diagnosed. These values approach the absolute risks of recurrent venous thromboembolism.[15-17] This implicates that clinicians should be aware of both arterial thromboembolism and recurrent venous thromboembolism, since both diseases are almost equally common in patients with previous venous thromboembolism. The risk of arterial thromboembolism was highest within the first year after venous thromboembolism. This early occurrence is in accordance with other studies.[3,9] Although the adjusted hazard ratio for subsequent arterial thromboembolism decreased from a statistically significant 2.6-fold (95% CI, 1.46-4.55; *P*-value, 0.001) increased risk in the first year of follow-up to a non-statistically significant 1.5-fold (95% CI, 0.95-2.41; *P*-value, 0.08) increased risk in the following years, a similar tendency was found in the study of Sørensen et al.[3]

The high risk of arterial thromboembolism in subjects with an unprovoked venous event compared to those with a provoked event suggests that a joint mechanism causes events in both venous and arterial systems. Our finding that the relation between arterial and venous thromboembolism remains persistent after adjustment for cardiovascular risk factors supports this idea. Obesity is related to a higher risk of arterial[18,19] and venous thromboembolism.[20-24] This might partly explain the relation between arterial and venous thromboembolism through endothelial damage and/or the related changes in the levels of procoagulant proteins.[25-32] Unfortunately, data on weight and height were not available for all the 40,856 participants in our cohort.

Our study has both strengths and limitations. Strengths are the large population-based cohort, the long follow-up time, the prospectively collected data on arterial events, the estimation of absolute risks, the possibility to analyze confounding cardiovascular risk factors, and the adjustments we made for age and sex in all analyses. A possible limitation of our study is that the data on cardiovascular risk factors were collected using self-reported histories. A certain degree of

misclassification might have occurred, which may have caused bias. Exact start- and stopping dates of anticoagulation were not available and hence not used in our analyses. However, since use of anticoagulation reduces the risk of arterial thromboembolism,[33] it is reasonable to have caused an underestimation of the strength of the association between arterial and venous thromboembolism in our study.

Interestingly, among the subjects with venous thromboembolism, subjects with pulmonary embolism seemed not to be at increased risk of arterial thromboembolism. A possible explanation for this finding could be that subjects with pulmonary embolism had a reduced life expectancy, and therefore did not have the opportunity to be at risk for arterial thromboembolism. However, compared to subjects with deep vein thrombosis, the life expectancy of patients with pulmonary embolism was not shorter in our cohort. Another explanation could be that pulmonary events were mainly provoked events, since provoked events did not increase the risk of arterial thromboembolism. Yet, the distribution of provoked versus unprovoked events were comparable in the subjects with deep vein thrombosis and those with pulmonary embolism. Klok *et al.* could not show a relation between pulmonary embolism and arterial thromboembolism either, but they did show an increased risk after unprovoked pulmonary embolism.[9] In our study, numbers were too small for this analysis.

The possibility that a higher risk of arterial thromboembolism after venous thromboembolism was spurious due to a hospitalization bias was ruled out as hazard ratios were not materially affected when we restricted the analysis to hard endpoints.

We conclude from this large cohort study that subjects with venous thromboembolism are at a high risk to develop arterial thromboembolism. This risk is especially high in the first year after venous thromboembolism and after an unprovoked event. The risk remains persistent after adjustment for age, sex, cardiovascular risk factors and previous arterial thromboembolism. Our findings implicate that, from now on, the clinical course of patients with venous thromboembolism should not only focus on the prevention of recurrent venous thromboembolism but also on the prevention of arterial thromboembolism.

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